REMARKS

Claims 1-14, 17-21, and 43-92 are pending in the application. Claims 1-5, 10, 14, 17, and 21 have been amended. Support for these amendments can be found in the application at, e.g., page 5, lines 2-22, page 10, lines 1-6, and page 27, lines 8-12. No new matter has been added by these amendments.

The Invention

The invention generally relates to profiles of polypeptide ligands that share the characteristic of being able to bind specifically to a particular multi-ligand binding receptor of a cell of interest. Generally, the polypeptide ligands are obtained by extraction from a ligand/receptor complex, then characterized and displayed or catalogued in a ligand profile. The invention is based, at least in part, on the inventors' discovery that certain ligand-binding systems within a cell can be used to identify proteins expressed in that cell. Each system contains one or more types of multi-ligand binding receptors that specifically bind in a highly reproducible manner to cellular polypeptide ligands present in a particular cell, and as such the set of ligands bound to such multi-ligand receptors largely reflects the set of proteins expressed in that cell.

The power of the cell's multi-ligand binding receptor systems, including the MHC class I and MHC class II receptor systems, is harnessed to identify native polypeptide ligands produced within a cell of interest. The polypeptide ligands so identified can be used to catalogue the proteins expressed and "turned over" in a cell for any particular cell type. Characteristic profiles or fingerprints of polypeptide ligands can be generated, for example, for given cell types, for diseased vs. normal cells, or for different metabolic or developmental states of a cell. Appropriate comparisons of the profiles can be used to identify cellular targets useful in diagnostics, drug screening and development, and developing therapeutic regimens.

Formal Drawings

On page 2 of the Office Action, the Examiner stated that applicants must submit corrected drawings for the application. Formal drawings are submitted with this response.

35 U.S.C. § 103(a)

Claims 1-14, 17-21, and 43-92 were rejected as allegedly obvious over Brusic et al. (1998) Nucleic Acids Res. 26:368 ("Brusic") in view of Jeff Seale (The GroEL Protein Interaction Database) ("Seale"), and further in view of Flanagan et al., U.S. Patent No. 5,795,734 ("Flanagan") and Duan et al. (1995) Proc. Natl. Acad. Sci. USA 92:6459 ("Duan").

Applicants traverse the rejection in view of the claim amendments and the following comments.

Each of the ligand profiles of independent claims 1-5, as amended, contains a representation of at least ten different polypeptide ligands that are produced in a given cell and that bind to a single type of multi-ligand binding receptor that is present in the same cell. The profiles of the claimed invention make use of the promiscuous binding properties of multi-ligand binding receptors (i.e., their ability to reproducibly bind to at least ten different polypeptide ligands in a cell) so as to create a polypeptide profile that is a reproducible characteristic of a given cell. The claimed ligand profiles do not encompass a profile that characterizes a cell merely based upon the ability of a receptor present on the surface of the cell to bind to peptides external to the cell (e.g., soluble peptides or peptides present on the surface of a different cell). Rather, the polypeptide ligands of the claimed ligand profiles are produced in the same cell that contains the multi-ligand binding receptor.

On pages 3-4 of the Office Action, the Examiner stated that

> the disclosed profile [of Brusic] of MHC class I receptor is characteristic of T-cell. This is suggested throughout the text of Brusic et al. as evidenced by reciting T-cells on page 368, paragraphs 1 and 2, page 369, left column, paragraph 1, page 370, left column, etc. etc. It is well-known that MHC class I is a characteristic of T-cells and the receptor binding profile is certainly characteristic of T-cell. It is also well-known that the receptor binding profile for a given cell type, such as T-cell, changes as environmental condition of the cell changes such as temperature, pH value, and the presence of regulatory molecules. Thus, the binding profile by Brusic et al. is at least characteristic of T-cell type.

The disclosure of Brusic was discussed at length during the undersigned's interview with Examiners Zhou and Borin on March 1, 2002. As explained by the undersigned during the interview, the MHCPEP database of Brusic is not a "ligand profile" of the presently claimed invention (i.e., a reproducible characteristic of a given cell wherein the polypeptide ligands of the

ligand profile and the multi-ligand binding receptor to which the polypeptide ligands bind are present in the same cell). Brusic describes a database that contains a description of over 13,000 peptide sequences that bind to a wide variety of MHC class I or class II molecules. MHC class I molecules are expressed on virtually all nucleated cells, and MHC class II molecules are expressed on B cells, macrophages, dendritic cells, endothelial cells, and a few other cells types. Brusic's database was compiled by analyzing published reports describing MHC class I or class II-binding peptides as well as by obtaining direct submissions of experimental data on such peptides (see Abstract of Brusic).

The listing of MHC-binding peptides provided by Brusic does not constitute a ligand profile that is a characteristic of a given cell, as is required by claims 1-5. Instead, the MHC-binding peptides described in Brusic's database were derived from experiments carried out using diverse cell types as well as using cell free assays (see "Method" section on page 368 of Brusic, describing the use of T cell activity assays as well as direct biochemical methods to characterize the binding of peptides to MHC molecules). In addition, Brusic's database contains MHC-binding data both for peptides that correspond to portions of naturally occurring proteins as well as for mutant peptides that have no naturally occurring counterpart (see, e.g., Brusic, page 369, column 2). Clearly, the over 13,000 peptides described by Brusic are not collectively produced within any given cell, do not bind to a single type of multi-ligand binding receptor present in the cell, and do not constitute a reproducible characteristic of the cell. They thus do not constitute a ligand profile of the claimed invention.

The Examiner suggested that Brusic discloses a profile characteristic of a T cell. However, the database of Brusic does not constitute a "ligand profile," as that phrase is used in the claimed invention, that is characteristic of a T cell. A T cell receptor is expressed on the surface of a T cell and binds to the complex of a small peptide bound to an MHC molecule on the surface of an opposing cell. This binding event provides a specific signal to the T cell that triggers its activation. In such a binding event, neither the small peptide nor the MHC molecule is present in the same cell as the T cell receptor. Instead, the small peptide and the MHC molecule are present on a cell separate from the T cell. Accordingly, a listing of peptides that, when presented in the context of an MHC molecule, bind to a T cell receptor does not constitute a ligand profile of the claimed invention.

The application also includes claims directed to methods of generating and using ligand profiles as well as sets of ligand profiles. These claims have been amended so as to require that the profiles contain at least ten different native polypeptide ligands (proteins or peptide intermediates produced within a given cell). Brusic does not describe creating a ligand profile of a cell by characterizing at least ten different polypeptide ligands that are produced in the cell and bind to a single type of multi-ligand binding receptor in the same cell.

Brusic's description of peptide sequences that bind to MHC molecules provides no motivation whatsoever to create a profile of at least ten different polypeptide ligands that are produced in a given cell and that bind to a single type of multi-ligand binding receptor in the same cell. Although Brusic provides a motivation to characterize MHC molecules by cataloging peptide sequences (from multiple cell types) that can bind to specific MHC molecules, the reference provides no motivation to create a ligand profile that characterizes a given cell based upon the ability of polypeptide produced in the cell to bind to a single type of MHC molecule (or other multi-ligand binding receptor) in the same cell.

For the reasons provided herein, applicants respectfully submit that nothing in Brusic, either alone or when combined with the other cited references, describes or suggests the ligand profiles and methods of the invention. Based upon the interview with the Examiner, it is the undersigned's understanding that the amendments and comments provided herein clearly distinguish the claimed invention from the disclosure of Brusic. Like Brusic, the remaining cited references (Seale, Flanagan, and Duan) have the common feature of characterizing a protein (or a class of proteins) by describing one or more polypeptides or peptides that interact (directly or indirectly) with the protein. However, none of the cited references suggests characterizing a cell by means of creating a profile of polypeptide ligands produced within that cell. It is applicants' understanding, based upon the undersigned's interview with the Examiner, that the rejections involving the secondary references will be overcome once the patentability of the claimed invention over Brusic has been established.

CONCLUSIONS

Applicants submit that all grounds for rejection have been overcome, and that all claims are now in condition for allowance, which action is requested. Attached is a marked-up version

of the changes being made by the current amendments. The attached pages are captioned "Version with markings to show changes made." Also attached is a listing of the claims pending in the application upon entry of the amendments presented herein.

Enclosed is an RCE transmittal letter, a Petition for One Month Extension of Time, and a check for the RCE fee and the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 08191-008003.

Respectfully submitted,

Date: April 30, 2002

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Version with Markings to Show Changes Made

In the Claims:

Claims 1-5, 10, 14, 17, and 21 have been amended as follows:

1. (Amended) A ligand profile which is characteristic for a given cell, the ligand profile comprising a representation of at least ten different polypeptide ligands produced in the cell, wherein all of the at least ten different polypeptide ligands [all of which] bind to a single type of multi-ligand binding receptor present in the cell, wherein the representation characterizes each individual ligand based upon at least three physical or chemical attributes; provided that, if the multi-ligand binding receptor is an MHC class I or class II receptor, at least 500 polypeptide ligands are represented in the ligand profile; and further provided that the ligand profile is a reproducible characteristic of the cell.

2. (Amended) A ligand profile which is characteristic for a given cell, the ligand profile comprising a representation of at least ten different polypeptide ligands produced in the cell, wherein all of the at least ten different polypeptide ligands [all of which] bind to a single type of multi-ligand binding receptor present in the cell, wherein the representation characterizes each individual ligand based upon at least two physical or chemical attributes, one of said attributes being mass or mass-to-charge ratio; provided that, if the multi-ligand binding receptor is an MHC class I or class II receptor, at least 500 polypeptide ligands are represented in the ligand profile; and further provided that the ligand profile is a reproducible characteristic of the cell.

3. (Amended) A ligand profile which is characteristic for a given cell, the ligand profile comprising a representation of at least ten different polypeptide ligands produced in the cell, wherein all of the at least ten different polypeptide ligands [all of which] bind to a single type of multi-ligand binding receptor present in the cell, wherein the representation characterizes each individual ligand based upon at least one physical or chemical attribute, the at least one physical or chemical attribute comprising amino acid sequence; provided that, if the multi-ligand binding receptor is an MHC class I or class II receptor, at least 50 polypeptide ligands are represented in

the ligand profile; and further provided that the ligand profile is a reproducible characteristic of the cell.

4. (Amended) A ligand profile which is characteristic for a given cell, the ligand profile comprising ion fragmentation patterns for at least ten different polypeptide ligands produced in the cell, wherein all of the at least ten different polypeptide ligands [all of which polypeptide ligands] bind to a single type of multi-ligand binding receptor present in the cell; provided that, if the multi-ligand binding receptor is an MHC class I or class II receptor, at least 100 polypeptide ligands are represented in the ligand profile; and further provided that the ligand profile is a reproducible characteristic of the cell.

5. (Amended) A ligand profile which is characteristic for a given cell, the ligand profile comprising amino acid sequences of at least ten different polypeptide ligands produced in the cell and having distinct core peptides, wherein all of the at least ten different polypeptide ligands [all of which ligands] bind to a single type of multi-ligand binding receptor present in the cell; provided that, if the multi-ligand binding receptor is an MHC class I or class II receptor, at least 100 polypeptide ligands are represented in the ligand profile; and further provided that the ligand profile is a reproducible characteristic of the cell.

10. (Amended) A method of generating a reproducible ligand profile for a given cell type, which cell type comprises a selected type of multi-ligand binding receptor, the method comprising:

(a) providing a first sample of the given cell type, wherein the first sample comprises a first plurality of at least ten different native polypeptide ligands bound to the selected type of multi-ligand binding receptor;

(b) isolating the selected type of multi-ligand binding receptor from the first sample;

(c) separating the first plurality of ligands from the selected type of multi-ligand binding receptor;

(d) fractionating the first plurality of ligands;

(e) generating a first profile distinguishing among the first plurality of ligands on the basis of at least one chemical or physical attribute;

(f) providing a second sample of the given cell type, the second sample being essentially identical to the first sample, wherein the second sample comprises a second plurality of at least ten different native polypeptide ligands bound to the selected type of multi-ligand binding receptor;

(g) isolating the selected type of multi-ligand binding receptor from the second sample;

(h) separating the second plurality of ligands from the selected type of multi-ligand binding receptor;

(i) fractionating the second plurality of ligands;

(j) generating a second profile distinguishing among the second plurality of ligands on the basis of the at least one chemical or physical attribute; and

(k) confirming that the first profile and the second profile are essentially identical, and together represent a reproducible ligand profile for the given cell type.

14. (Amended) A method of generating a ligand profile for a given type of cell, comprising:

(a) providing a sample of lysate of the given type of cell, wherein the sample comprises a first plurality of at least ten different native polypeptide ligands bound to a first type of multi-ligand binding receptor and a second plurality of at least ten different native polypeptide ligands bound to a second type of multi-ligand binding receptor;

(b) isolating the first and second types of multi-ligand binding receptors from the sample;

(c) separating the first plurality of ligands from the first type of multi-ligand binding receptor and the second plurality of ligands from the second type of multi-ligand binding receptor;

(d) fractionating the first plurality of ligands and the second plurality of ligands; and

(e) generating a first profile distinguishing among the first plurality of ligands on the basis of at least one chemical or physical attribute and a second profile distinguishing among the second plurality of ligands on the basis of the same at least one chemical or physical attribute.

17. (Amended) A method of comparing a first cell sample to a reference cell sample, comprising:

(a) producing a first ligand profile by a method comprising:

(i) providing a first cell sample comprising a given type of multi-ligand binding receptor bound to a first set of at least ten different native polypeptide ligands;

(ii) isolating the given type of multi-ligand binding receptor and the first set of ligands from the first cell sample;

(iii) separating the first set of ligands from the given type of multi-ligand binding receptor;

(iv) generating a first ligand profile distinguishing among the first set of ligands on the basis of at least one chemical or physical attribute;

(b) providing a reference ligand profile representing a second set of at least ten different native polypeptide ligands extracted from the given type of multi-ligand binding receptor of a reference cell sample, wherein the reference ligand profile distinguishes among the second set of polypeptide ligands on the basis of the at least one chemical or physical attribute; and

(c) comparing the first ligand profile to the reference ligand profile, in order to identify differences or similarities between the first cell sample and the reference cell sample.

21. (Amended) A set of ligand profiles, comprising

(a) a first ligand profile comprising a first representation of a first plurality of at least ten different native polypeptide ligands, all of which bind to at least one multi-ligand binding receptor of a first cell, wherein the first representation distinguishes among the members of the first plurality of ligands based upon at least one physical or chemical attribute; and

(b) a second ligand profile comprising a second representation of a second plurality of at least ten different native polypeptide ligands, all of which bind to the at least one type of multi-ligand binding receptor of a second cell, wherein the second representation distinguishes among the second plurality of ligands based upon the at least one physical or chemical attribute;

provided that (i) the first cell differs from the second cell in a parameter selected from the group consisting of genetic background, culture conditions, genetic background plus culture

conditions, *in vivo* exposure to a test compound, and genetic background plus *in vivo* exposure to a test compound; and (ii) any significant difference between the first and the second ligand profiles is attributable to that parameter.

Pending Claims

1. A ligand profile which is characteristic for a given cell, the ligand profile comprising a representation of at least ten different polypeptide ligands produced in the cell, wherein all of the at least ten different polypeptide ligands bind to a single type of multi-ligand binding receptor present in the cell, wherein the representation characterizes each individual ligand based upon at least three physical or chemical attributes; provided that, if the multi-ligand binding receptor is an MHC class I or class II receptor, at least 500 polypeptide ligands are represented in the ligand profile; and further provided that the ligand profile is a reproducible characteristic of the cell.

2. A ligand profile which is characteristic for a given cell, the ligand profile comprising a representation of at least ten different polypeptide ligands produced in the cell, wherein all of the at least ten different polypeptide ligands bind to a single type of multi-ligand binding receptor present in the cell, wherein the representation characterizes each individual ligand based upon at least two physical or chemical attributes, one of said attributes being mass or mass-to-charge ratio; provided that, if the multi-ligand binding receptor is an MHC class I or class II receptor, at least 500 polypeptide ligands are represented in the ligand profile; and further provided that the ligand profile is a reproducible characteristic of the cell.

3. A ligand profile which is characteristic for a given cell, the ligand profile comprising a representation of at least ten different polypeptide ligands produced in the cell, wherein all of the at least ten different polypeptide ligands bind to a single type of multi-ligand binding receptor present in the cell, wherein the representation characterizes each individual ligand based upon at least one physical or chemical attribute, the at least one physical or chemical attribute comprising amino acid sequence; provided that, if the multi-ligand binding receptor is an MHC class I or class II receptor, at least 50 polypeptide ligands are represented in the ligand profile; and further provided that the ligand profile is a reproducible characteristic of the cell.

4. A ligand profile which is characteristic for a given cell, the ligand profile comprising ion fragmentation patterns for at least ten different polypeptide ligands produced in the cell,

wherein all of the at least ten different polypeptide ligands bind to a single type of multi-ligand binding receptor present in the cell; provided that, if the multi-ligand binding receptor is an MHC class I or class II receptor, at least 100 polypeptide ligands are represented in the ligand profile; and further provided that the ligand profile is a reproducible characteristic of the cell.

5. A ligand profile which is characteristic for a given cell, the ligand profile comprising amino acid sequences of at least ten different polypeptide ligands produced in the cell and having distinct core peptides, wherein all of the at least ten different polypeptide ligands bind to a single type of multi-ligand binding receptor present in the cell; provided that, if the multi-ligand binding receptor is an MHC class I or class II receptor, at least 100 polypeptide ligands are represented in the ligand profile; and further provided that the ligand profile is a reproducible characteristic of the cell.

6. The ligand profile of claim 1, wherein the multi-ligand binding receptor is an MHC class I or MHC class II receptor.

7. The ligand profile of claim 1, wherein the multi-ligand binding receptor is not an MHC class I or MHC class II receptor.

8. The ligand profile of claim 1, wherein the multi-ligand binding receptor is a chaperone, a calnexin, a calreticutin, a mannosidase, a N-glycanase, a BIP, a grp94, a grp96, an E2 ubiquitin carrier protein, an E3 ubiquitin ligase, an unfoldase, a proteasome, a trafficking protein, or a retention protein.

9. The ligand profile of claim 1, combined with a second ligand profile, the second ligand profile (a) also being a reproducible characteristic of the given cell, and (b) comprising a representation of at least ten additional polypeptide ligands, all of which bind to a second type of multi-ligand binding receptor different from the first type of receptor.

10. A method of generating a reproducible ligand profile for a given cell type, which cell type comprises a selected type of multi-ligand binding receptor, the method comprising:

(a) providing a first sample of the given cell type, wherein the first sample comprises a first plurality of at least ten different native polypeptide ligands bound to the selected type of multi-ligand binding receptor;

(b) isolating the selected type of multi-ligand binding receptor from the first sample;

(c) separating the first plurality of ligands from the selected type of multi-ligand binding receptor;

(d) fractionating the first plurality of ligands;

(e) generating a first profile distinguishing among the first plurality of ligands on the basis of at least one chemical or physical attribute;

(f) providing a second sample of the given cell type, the second sample being essentially identical to the first sample, wherein the second sample comprises a second plurality of at least ten different native polypeptide ligands bound to the selected type of multi-ligand binding receptor;

(g) isolating the selected type of multi-ligand binding receptor from the second sample;

(h) separating the second plurality of ligands from the selected type of multi-ligand binding receptor;

(i) fractionating the second plurality of ligands;

(j) generating a second profile distinguishing among the second plurality of ligands on the basis of the at least one chemical or physical attribute; and

(k) confirming that the first profile and the second profile are essentially identical, and together represent a reproducible ligand profile for the given cell type.

11. The method of claim 10, wherein a second chemical or physical attribute of each ligand is determined subsequent to the fractionation steps, and is represented in the profiles.

12. The method of claim 11, wherein a third chemical or physical attribute of each ligand is determined subsequent to the fractionation steps, and is represented in the profiles.

13. The method of claim 10, wherein the isolating and separating steps are accomplished using appropriate columns arranged in an in-line system.

14. A method of generating a ligand profile for a given type of cell, comprising:

(a) providing a sample of lysate of the given type of cell, wherein the sample comprises a first plurality of at least ten different native polypeptide ligands bound to a first type of multi-ligand binding receptor and a second plurality of at least ten different native polypeptide ligands bound to a second type of multi-ligand binding receptor;

(b) isolating the first and second types of multi-ligand binding receptors from the sample;

(c) separating the first plurality of ligands from the first type of multi-ligand binding receptor and the second plurality of ligands from the second type of multi-ligand binding receptor;

(d) fractionating the first plurality of ligands and the second plurality of ligands; and

(e) generating a first profile distinguishing among the first plurality of ligands on the basis of at least one chemical or physical attribute and a second profile distinguishing among the second plurality of ligands on the basis of the same at least one chemical or physical attribute.

17. A method of comparing a first cell sample to a reference cell sample, comprising:

(a) producing a first ligand profile by a method comprising:

(i) providing a first cell sample comprising a given type of multi-ligand binding receptor bound to a first set of at least ten different native polypeptide ligands;

(ii) isolating the given type of multi-ligand binding receptor and the first set of ligands from the first cell sample;

(iii) separating the first set of ligands from the given type of multi-ligand binding receptor;

(iv) generating a first ligand profile distinguishing among the first set of ligands on the basis of at least one chemical or physical attribute;

(b) providing a reference ligand profile representing a second set of at least ten different native polypeptide ligands extracted from the given type of multi-ligand binding receptor of a

reference cell sample, wherein the reference ligand profile distinguishes among the second set of polypeptide ligands on the basis of the at least one chemical or physical attribute; and

(c) comparing the first ligand profile to the reference ligand profile, in order to identify differences or similarities between the first cell sample and the reference cell sample.

18. The method of claim 17, wherein the reference cell sample consists essentially of healthy cells of an animal and the first cell sample comprises cells suspected of being diseased.

19. The method of claim 17, wherein the first cell sample comprises cells cultured in the presence of a test compound, and the reference cell sample does not.

20. The method of claim 17, wherein the reference cell sample comprises cells cultured in the presence of a test compound, and the first cell sample does not.

21. A set of ligand profiles, comprising

(a) a first ligand profile comprising a first representation of a first plurality of at least ten different native polypeptide ligands, all of which bind to at least one multi-ligand binding receptor of a first cell, wherein the first representation distinguishes among the members of the first plurality of ligands based upon at least one physical or chemical attribute; and

(b) a second ligand profile comprising a second representation of a second plurality of at least ten different native polypeptide ligands, all of which bind to the at least one type of multi-ligand binding receptor of a second cell, wherein the second representation distinguishes among the second plurality of ligands based upon the at least one physical or chemical attribute;

provided that (i) the first cell differs from the second cell in a parameter selected from the group consisting of genetic background, culture conditions, genetic background plus culture conditions, *in vivo* exposure to a test compound, and genetic background plus *in vivo* exposure to a test compound; and (ii) any significant difference between the first and the second ligand profiles is attributable to that parameter.

43. The ligand profile of claim 2, wherein the multi-ligand binding receptor is an MHC class I or MHC class II receptor.

44. The ligand profile of claim 2, wherein the multi-ligand binding receptor is not an MHC class I or MHC class II receptor.

45. The ligand profile of claim 2, wherein the multi-ligand binding receptor is a chaperone, a calnexin, a calreticutin, a mannosidase, a N-glycanase, a BIP, a grp94, a grp96, an E2 ubiquitin carrier protein, an E3 ubiquitin ligase, an unfoldase, a proteasome, a trafficking protein, or a retention protein.

46. The ligand profile of claim 2, combined with a second ligand profile, the second ligand profile (a) also being a reproducible characteristic of the given cell, and (b) comprising a representation of at least ten additional polypeptide ligands, all of which bind to a second type of multi-ligand binding receptor different from the first type of receptor.

47. The ligand profile of claim 46, wherein the second type of multi-ligand binding receptor is an MHC class I or MHC class II receptor.

48. The ligand profile of claim 3, wherein the multi-ligand binding receptor is an MHC class I or MHC class II receptor.

49. The ligand profile of claim 3, wherein the multi-ligand binding receptor is not an MHC class I or MHC class II receptor.

50. The ligand profile of claim 3, wherein the multi-ligand binding receptor is a chaperone, a calnexin, a calreticutin, a mannosidase, a N-glycanase, a BIP, a grp94, a grp96, an E2 ubiquitin carrier protein, an E3 ubiquitin ligase, an unfoldase, a proteasome, a trafficking protein, or a retention protein.

51. The ligand profile of claim 3, combined with a second ligand profile, the second ligand profile (a) also being a reproducible characteristic of the given cell, and (b) comprising a representation of at least ten additional polypeptide ligands, all of which bind to a second type of multi-ligand binding receptor different from the first type of receptor.

52. The ligand profile of claim 51, wherein the second type of multi-ligand binding receptor is an MHC class I or MHC class II receptor.

53. The ligand profile of claim 4, wherein the multi-ligand binding receptor is an MHC class I or MHC class II receptor.

54. The ligand profile of claim 4, wherein the multi-ligand binding receptor is not an MHC class I or MHC class II receptor.

55. The ligand profile of claim 4, wherein the multi-ligand binding receptor is a chaperone, a calnexin, a calreticutin, a mannosidase, a N-glycanase, a BIP, a grp94, a grp96, an E2 ubiquitin carrier protein, an E3 ubiquitin ligase, an unfoldase, a proteasome, a trafficking protein, or a retention protein.

56. The ligand profile of claim 4, combined with a second ligand profile, the second ligand profile (a) also being a reproducible characteristic of the given cell, and (b) comprising a representation of at least ten additional polypeptide ligands, all of which bind to a second type of multi-ligand binding receptor different from the first type of receptor.

57. The ligand profile of claim 56, wherein the second type of multi-ligand binding receptor is an MHC class I or MHC class II receptor.

58. The ligand profile of claim 5, wherein the multi-ligand binding receptor is an MHC class I or MHC class II receptor.

59. The ligand profile of claim 5, wherein the multi-ligand binding receptor is not an MHC class I or MHC class II receptor.

60. The ligand profile of claim 5, wherein the multi-ligand binding receptor is a chaperone, a calnexin, a calreticutin, a mannosidase, a N-glycanase, a BIP, a grp94, a grp96, an E2 ubiquitin carrier protein, an E3 ubiquitin ligase, an unfoldase, a proteasome, a trafficking protein, or a retention protein.

61. The ligand profile of claim 5, combined with a second ligand profile, the second ligand profile (a) also being a reproducible characteristic of the given cell, and (b) comprising a representation of at least ten additional polypeptide ligands, all of which bind to a second type of multi-ligand binding receptor different from the first type of receptor.

62. The ligand profile of claim 61, wherein the second type of multi-ligand binding receptor is an MHC class I or MHC class II receptor.

63. The method of claim 10, wherein the selected type of multi-ligand binding receptor is an MHC class I or MHC class II receptor.

64. The method of claim 10, wherein the selected type of multi-ligand binding receptor is a chaperone, a calnexin, a calreticutin, a mannosidase, a N-glycanase, a BIP, a grp94, a grp96, an E2 ubiquitin carrier protein, an E3 ubiquitin ligase, an unfoldase, a proteasome, a trafficking protein, or a retention protein.

65. The method of claim 10, wherein the at least one chemical or physical attribute comprises hydrophobicity or charge.

66. The method of claim 10, wherein the at least one chemical or physical attribute comprises mass-to-charge ratio.

67. The method of claim 10, wherein the at least one chemical or physical attribute comprises amino acid sequence.

68. The method of claim 14, wherein the first type of multi-ligand binding receptor is an MHC class I or MHC class II receptor.

69. The method of claim 14, wherein the first type of multi-ligand binding receptor is a chaperone, a calnexin, a calreticutin, a mannosidase, a N-glycanase, a BIP, a grp94, a grp96, an E2 ubiquitin carrier protein, an E3 ubiquitin ligase, an unfoldase, a proteasome, a trafficking protein, or a retention protein.

70. The method of claim 14, wherein the at least one chemical or physical attribute comprises hydrophobicity or charge.

71. The method of claim 14, wherein the at least one chemical or physical attribute comprises mass-to-charge ratio.

72. The method of claim 14, wherein the at least one chemical or physical attribute comprises amino acid sequence.

73. The method of claim 17, comprising the further steps of selecting a ligand which is represented in one profile but not in the other, and identifying the amino acid sequence of the ligand.

74. The method of claim 17, wherein the given type of multi-ligand binding receptor is an MHC class I or MHC class II receptor.

75. The method of claim 17, wherein the given type of multi-ligand binding receptor is a chaperone, a calnexin, a calreticutin, a mannosidase, a N-glycanase, a BIP, a grp94, a grp96, an

E2 ubiquitin carrier protein, an E3 ubiquitin ligase, an unfoldase, a proteasome, a trafficking protein, or a retention protein.

76. The method of claim 17, wherein the at least one chemical or physical attribute comprises hydrophobicity or charge.

77. The method of claim 17, wherein the at least one chemical or physical attribute comprises mass-to-charge ratio.

78. The method of claim 17, wherein the at least one chemical or physical attribute comprises amino acid sequence.

79. The set of ligand profiles of claim 21, wherein the at least one type of multi-ligand binding receptor is an MHC class I or MHC class II receptor.

80. The set of ligand profiles of claim 21, wherein the at least one type of multi-ligand binding receptor is a chaperone, a calnexin, a calreticutin, a mannosidase, a N-glycanase, a BIP, a grp94, a grp96, an E2 ubiquitin carrier protein, an E3 ubiquitin ligase, an unfoldase, a proteasome, a trafficking protein, or a retention protein.

81. The set of ligand profiles of claim 21, wherein the first cell is from a healthy individual and the second cell is from an individual suffering from a given disease.

82. The set of ligand profiles of claim 81, wherein the individuals are humans.

83. The set of ligand profiles of claim 21, wherein the first cell is from healthy tissue and the second cell is from diseased tissue.

84. The ligand profile of claim 8, wherein the multi-ligand binding receptor is a chaperone selected from the group consisting of a chaperonin, hsp60, hsp65, hsp70, hsp90, hsp25, and hsp100.

85. The ligand profile of claim 45, wherein the multi-ligand binding receptor is a chaperone selected from the group consisting of a chaperonin, hsp60, hsp65, hsp70, hsp90, hsp25, and hsp100.

86. The ligand profile of claim 50, wherein the multi-ligand binding receptor is a chaperone selected from the group consisting of a chaperonin, hsp60, hsp65, hsp70, hsp90, hsp25, and hsp100.

87. The ligand profile of claim 55, wherein the multi-ligand binding receptor is a chaperone selected from the group consisting of a chaperonin, hsp60, hsp65, hsp70, hsp90, hsp25, and hsp100.

88. The ligand profile of claim 60, wherein the multi-ligand binding receptor is a chaperone selected from the group consisting of a chaperonin, hsp60, hsp65, hsp70, hsp90, hsp25, and hsp100.

89. The method of claim 64, wherein the selected type of multi-ligand binding receptor is a chaperone selected from the group consisting of a chaperonin, hsp60, hsp65, hsp70, hsp90, hsp25, and hsp100.

90. The method of claim 69, wherein the first type of multi-ligand binding receptor is a chaperone selected from the group consisting of a chaperonin, hsp60, hsp65, hsp70, hsp90, hsp25, and hsp100.

91. The method of claim 75, wherein the given type of multi-ligand binding receptor is a chaperone selected from the group consisting of a chaperonin, hsp60, hsp65, hsp70, hsp90, hsp25, and hsp100.

92. The set of ligand profiles of claim 80, wherein the at least one type multi-ligand binding receptor is a chaperone selected from the group consisting of a chaperonin, hsp60, hsp65, hsp70, hsp90, hsp25, and hsp100.